Scientific Inquiry and Review (SIR)
Volume 6 Issue 2, 2022
ISSN $_{(P)}$: 2521-2427, ISSN $_{(E)}$: 2521-2435
Homepage: https://journals.umt.edu.pk/index.php/SIR

Article QR

Title: **Sources and Chemistry of Flavonoids: An Overview of their Biological and Therapeutic Potential**

Author (s): Waqar Mirza[1], Shabbir Hussain[2], Muhammad Ahmad[3], Mufliha Murtaza[1], Abdur Rauf[4], Ammara Aslam[1], Gull Yasmeen[1], Tania Arif[2], Ansa Nazir[1], Irum Hanif[1]

Affiliation (s): [1]Lahore Garrison University, Lahore, Pakistan
[2]Khwaja Fareed University of Engineering and Information Technology, Rahim Yar Khan, Pakistan.
[3]Division of Science and Technology, University of Education, Lahore, Pakistan
[4]University of Sahiwal, Sahiwal, Pakistan

DOI: https://doi.org/10.32350/sir.62.03

History: Received: November 7, 2022, Reviewed: May 17, 2022, Accepted: May 25, 2022

Citation: Mirza W, Hussain S, Ahmed M, et al. Sources and Chemistry of flavonoids: An overview of their biological and therapeutic potential. *Sci Inquiry Rev.* 2022;6(2):00-00. https://doi.org/10.32350/sir.62.03

Conflict of Interest: Author(s) declared no conflict of interest

A publication of
The School of Science
University of Management and Technology, Lahore, Pakistan

Sources and Chemistry of Flavonoids: An Overview of their Biological and Therapeutic Potential

Waqar Mirza[1], Shabbir Hussain[2*], Muhammad Ahmad[3], Mufliha Murtaza[1], Abdur Rauf[4], Ammara Aslam[1], Gull Yasmeen[1], Tania Arif[2], Ansa Nazir[1], Irum Hanif[1]

[1]Department of Chemistry, Lahore Garrison University, DHA Phase VI, Lahore, Pakistan
[2]Institute of Chemistry, Khwaja Fareed University of Engineering and Information Technology, Rahim Yar Khan 64200, Pakistan.
[3]Department of Chemistry, Division of Science and Technology, University of Education, Lahore 54770, Pakistan
[4]Department of Chemistry, University of Sahiwal, Sahiwal 57000, Pakistan

* shabbir.hussain@kfueit.edu.pk

ABSTRACT

Flavonoids are natural polyphenolic compounds responsible for the taste and color of medicinal plants, herbs, fruits, and vegetables. Fruits (for example, berries, cherries, plums, apples, lemons, oranges, and grapes) and vegetables (for example., broad beans, olives, onions, spinach, and shallot) are the main sources of flavonoids. They also exist abundantly in cocoa products, black and green tea, red wine, red pepper, chamomile, celery, parsley, ginkgo, and mint. Flavonoid derivatives could also be synthesized through esterification, halogenation, alkoxylation, alkylation, aromatic hydroxylation, acylation, and conjugation with various organic compounds. Flavonoids could also be supplemented as a staple of food which act as a nutraceutical agents and play an important role in the human diet. They possess diverse biological activities including anti-inflammation, anti-oxidation, anti-cancer, anti-diabetes, anti-obesity, antimutagenic, neuroprotective, and also have beneficial effects on oxidative stress, inflammation, insulin resistance, lipid metabolism, and neurodegenerative diseases (for example., amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease and Alzheimer's disease). Flavonoids contain a 15-carbon skeleton; the basic structure consists of a flavan nucleus, a combination of two benzene and one pyran ring. They are divided into eight important groups namely flavones, flavanols, isoflavones, flavan-3-ols, flavanonols, anthocyanidins, chalcones, and flavanones. A structure-activity relationship exists between flavonoids and their antioxidant activities. Flavonoids are effective in chelating metal ions and *scavenging free radicals. Their antioxidant properties are governed by their –OH groups, differences in hydrophobicity, and molecular planarity.*

Keywords: antioxidant potential, flavonoids, structure-activity relationship, working mechanism

INTRODUCTION

Plants find an immense nutritional [1, 2] and medicinal [3-5] value especially due to the presence of their antioxidant contents [6-8]. A lot of natural compounds are derived from dietary or medicinal plants and applied in clinical research for the treatment of numerous diseases; this trend has gained significant importance day by day [9, 10]. The important plant constituents include flavanones, flavones, anthocyanins, and catechins which are polyphenolic compounds [11, 12] and demonstrate many biochemical and pharmacological applications including antidiabetic, anti-inflammatory, antimicrobial, immunomodulatory, gastroprotective, neuroprotective, antioxidant, and also have a regulatory role on the hormones [13].

Flavonoids are powerful antioxidants [14] which provide protection to plants against harsh environmental conditions [15]. Therefore, a large number of experimental and epidemiological studies have been conducted to evaluate their beneficial effects in multiple chronic and acute disorders reported in the humans [16]. Flavonoids play an important role in acclimatization, freezing tolerance, and resistance against drought [17]. They have accredited positive health effects on humans and animals and most recent studies are focusing on their applications in chemoprevention and disease therapy [18, 19]. Dixon *et al*. discussed the role of plant flavonoids and isoflavonoids in neuroscience in the human beings and agricultural sector [19]. Kumar and coworkers reported the flavonoids' as protective agents against human diseases and discussed their role in plants [20]. Panche and colleagues elaborated the detailed applications of flavonoids and the role of plant secondary metabolites to treat Alzheimer's disease and the involved mechanism [21].

Hence, this current study was conducted to overview the natural and synthetic sources of flavonoids, their chemistry, and antioxidant/disease potential.

2. SOURCES OF NATURAL FLAVONOIDS

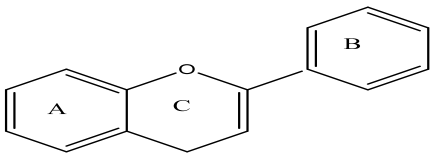
Flavonoids are a class of polyphenolic compounds which occur abundantly in naturally occurring plants [22, 23]. They are synthesized as bioactive secondary metabolites [15] and impart color, taste, and pharmacological activities [24]. There are almost six thousand flavonoids which are responsible for the colorful pigments of medicinal plants, herbs, fruits, and vegetables *etc* [25]. Fruits and vegetables are the main sources of flavonoids [26]; they also exist abundantly in cocoa products [27], black and green tea [28] and red wine [29]. Berries [30], cherries, plums [31], and apples [14] are considered as richest in flavonoid contents; however, amounts of flavonoids in tropical fruits are low [32]. Among vegetables, broad beans [33], olives [34], onions [35], spinach [36], and shallot [37] are the richest in flavonoids. Bioactive flavonoids are primarily found in edible parts of plants, although a few of them are also found in non-edible parts (*i.e*., stem, root, and leaves) of plants. In the majority of angiosperm families, several flavonoids could easily be recognized as floral pigments. Major sources of flavones include red pepper, chamomile, celery, parsley, ginkgo, and mint. Another significant class namely flavanones, is typically found in all citrus fruits, including lemons, oranges, and grapes [38].

3. SOURCES OF SYNTHETIC FLAVONOIDS

With the development of synthetic biology and the clarification of the biosynthetic pathway of flavonoids, synthetic metabolic engineering methods have been applied with microorganisms as hosts to produce the flavonoids [39]. Although flavonoids have significant biological importance, they also have certain limitations such as a lack of selectivity and low oral bioavailability. Several flavonoid derivatives have been produced through esterification, halogenation, alkoxylation, alkylation, aromatic hydroxylation, acylation, and conjugation with various organic compounds [40]. Chalcones and dihydrochalcones are the major precursors in flavonoid synthesis. The condensation of 2-hydroxyacetophenones with benzaldehydes under basic or acidic conditions, for example, is the most primary method of producing chalcones and flavanones. There are also asymmetric techniques that frequently involve flavone/isoflavone/chalcone epoxides as intermediates. 4-iminoflavones, 4-thioflavones, and flavones could be synthesized by the substitution of different halogens, methyl, methoxy, and nitro groups from the A, B, and AB rings of the respective precursors [41].

4. STRUCTURE AND CLASSIFICATION OF FLAVONOIDS

Flavonoid are the compounds based on a 15-carbon skeleton. As shown in **Figure 1**, the flavonoid skeleton consists of 2 phenyl rings (i.e. A- and B-ring) linked by three carbon bridge at the simplest level (C-ring) [42, 43]. Their biosynthesis process has been already reported in the previous literature [39, 44]. Mostly, flavonoids are present as glycosides in vacuoles of flower, leaves, stems or roots [42, 45]. In addition, aglycones are more active than their corresponding glycosides as antioxidants [46, 47]. The basic structure consists of a flavan nucleus, a combination of two benzene and one pyran rings [20, 22]. Therefore, the distinct compounds vary by the substitution design of rings A and B [48].



Flavonoids
(general formula)

Fig 1. General structure of flavonoids

Flavonoids are divided into eight important groups; i) flavones, ii) flavanols, iii) isoflavones, iv)flavan-3-ols, v) flavanonols, vi) anthocyanidins, vii) chalcones, and viii) flavanones [49, 50]. The classification is based on the central pyran ring's oxidation state [51, 52]. The pyran structure ring is exposed in chalcones, and the furan structure ring is detected in aurones [53]. Due to the immense need to review this flavonoid structure, this current study explains the significance of each flavonoids, its kinds and further classes.

i) Flavone: Flavones are similar to flavonols. Both contain a double bond between carbon-2 and carbon-3 whereas the flavones have no hydroxyl group at C-3 [54]. This basic distinction between flavones and flavonols tend to have numerous applications in various industries [55].

ii) Flavanols: In the C-3 position, flavanols have a hydroxyl group. The most popular flavanols in fruits and vegetables include Fisetin, Quercetin, Kaempferol, and Myricetin [56, 57]. There are also other flavanols that could be contained in limited amounts in grains, leafy greens, and herbs [58]. Flavanols are a type of flavonoids having a backbone of 3-hydroxyflavone [54].

iii) Isoflavonoids: Isoflavones are the isomers of the flavone with a heterocyclic ring linked to the position of carbon-2 and carbon-3 [59]. The Leguminosae family is the principal source of isoflavonoids [60]. The basic molecules present in soybean seeds are Genistein and Daidzein [61, 62].

iv) Flavan-3-ole: Flavan-3-ole forms a set of hydroxyl bonds with C-ring at 3rd position. Unlike many other flavonoids, double bond is not present between carbon-2 and carbon-3 [58]. Green tea is derived from *Camellia sinesis* leaves which hold polyphenolic flavonoids as catechin-3-Gallate (ECG) [63]. Cacao beans also contain the monomeric flavonoids [64].

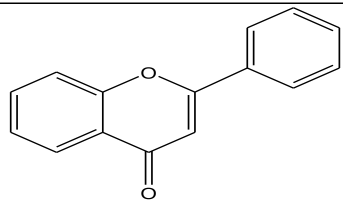
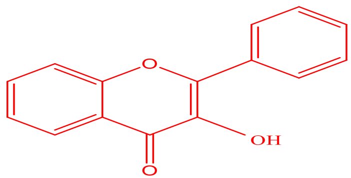
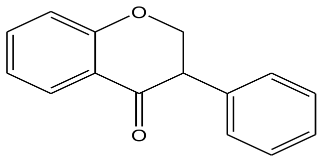
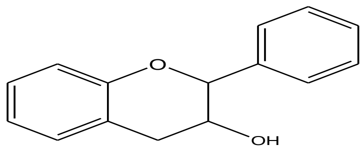
v) Flavanonols: The -OH group is located at C-3 in such flavonoids, and the O-atom is placed at C-4 of the ring [20, 51]. This group contains the flavonoids taxifolin, stilbene and silybin. Naturally, they occur as glycosides of dihydro-flavonol [65]. The rhizomes of *Smilax glabra* was found to contain 5 dihydro-flavonol glycosides including (2R, 3R)-taxifolin-3'-O-beta-D-pyranglucoside, isoastilbin neoisoastilbin, neoastilbin, and astilbin [66].

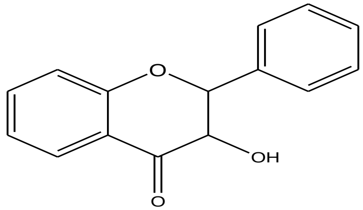
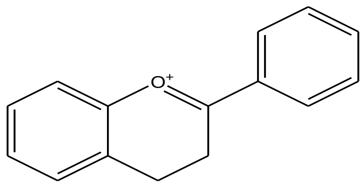
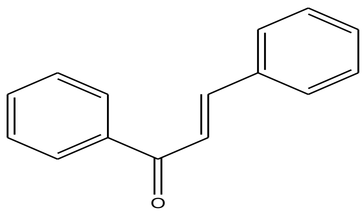
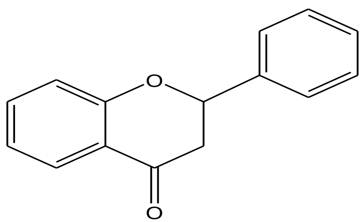
vi) Anthocyanins: They are soluble in water and have red, blue, and purple pigments which are accountable for the colors of fruits, vegetables, and flowers [67]. Pro-anthocyanidins are primarily found in grapes. [68]. Several forms of catechin and epicatechin flavonoids, oligomers or dimers, and gallic acid esters exist in plant materials. Compounds of the proanthocyanidin type include cyanidin, malvidin, pelargonidin, peonidin, petunidin, and delphinidinidin [69].

vii) Chalcones: They might also be called as flavonoids that are open chained. The 4,2',4',6'-tetrahydroxychalcone has been characterized as a pioneer for a wide variety of flavonoids [44]. Phloridzinis is an important example of chalcones. They are immensely found in large quantities in tomatoes, fruits (such as pear and bearberries), and some wheat products [70, 71].

viii) Flavanones: Flavanones, naringenin, naringin, hesperetin, and hesperidin cause an unpleasant sense of taste of the juice and skin of citrus fruits [72]. These are often known as dihydroxyflavones [58]. **Table 1** summarizes the various classes of flavonoids along with their structural formulae and examples.

Table 1: Various Classes of Flavonoids along with Their Structural Formulae and Examples

Type	Structural formula	Examples	References
Flavones		chrysin, baicalin, wogonin, tangeritinandapigenin	[73-75]
Flavonols		apigenin, luteolin and baicalein quercetin and luteolin	[58]
Isoflavonoids		Genistein and daidzein	[61]
Flavan-3-ols		Epicatechin (EC), Epigallocatechin (EGC), Epicatechin-3-Gallate (ECG) and Epigallocatechin-3-Gallate (EGCG)	[63]

Type	Structural formula	Examples	References
Flavanonols		taxifolin, astilbin and silibyn	[65]
Anthocyanin		Cyanidins, malvidin, palargenidin and peonodin	[69]
Chalcones		phloridzin, arbutin, phloretin and chalconaringenin. Chalcones	[70, 71]
Flavanones		naringenin, naringin, hesperetin, hesperidin	[58]

5. ANTIOXIDANT PROPERTIES OF FLAVONOIDS

Plant flavonoids are one of the most studied bioactive antioxidant and pro-oxidant compounds [76]. They are an essential part of our daily lives. Antioxidants work by delaying, preventing, and removing oxidative damage to a targeted molecule [77, 78].

5.1 Action Mechanism

The action mechanism of flavonoids might include: i) elimination or blockage of free radicals, ii) metal-based chelation, iii) suppression of enzymes linked to the production of free radicals and iv) stimulation of antioxidant enzymes in the body (**Figure 2**) [79, 80].

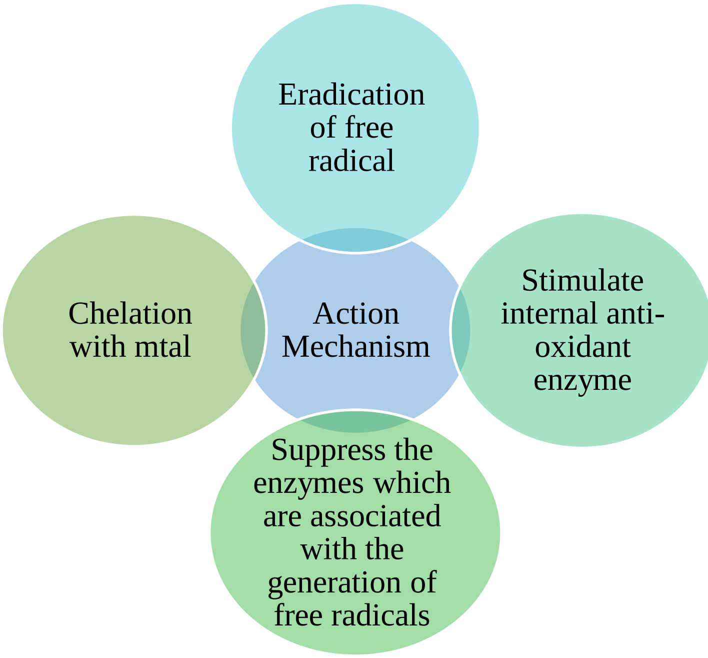


Fig 2. Action mechanism of flavonoid

Flavonoids are effective in chelating iron and scavenging free radicals [81]. Radicals may be generated in two ways: i) chemically or enzymatically (by xanthine/xanthine oxidase or reductase) and ii) by transition metal alone (or in conjunction with a reducing agent such as ascorbate non-enzymatically) [82]. Flavonoids scavenge radical oxygen species (ROS) directly. They would instantly chelate free radicals by donating a H-atom or by performing a one-electron transfer [83]. Chelation could be accomplished either by metal chelation or by using a transition metal part for chelation. Flavonoids can chelate or bind to metallic ions in the body of humans, preventing the body from many further complications. In particular, they have the potential to chelate trace metal ions such as Fe^{2+} and Cu^{+}, which are critical in free radical production and oxygen metabolism [84]. They could also bind transition metals and scavenge radicals directly. Free radical-producing enzymes such as lipoxygenase, xanthine oxidase, and protein kinase C are inhibited. The NADPH (nicotinamide adenine dinucleotide phosphate) oxidase, mitochondrial succinoxidase, microsomal monooxygenase, and cyclooxygenase allow them to function as an intracellular antioxidant [84]. The most effective defense enzymes against intracellular toxicants and xenobiotics are phase II metabolising enzymes (such as methyltransferases, glutathione *S*-transferases, *N*-acetyl transferases, sulfotransferases, and UDP-glucuronosyl transferases)[85].

The mechanism involves the donation of an H-atom from –OH group to a free radical molecule to stabilize it and thus a stable flavonoid phenoxy radical is generated. Consequently, this stable molecule would react with another radical (Alkoxyl (RO*)) having a stable quinine [86]. The location of the hydroxyl group affects more specifically on antioxidant action as compared to the total number of OH-groups present in the compound [87]. Both O_2 and N_2-centered free radicals could be scavenged by the B-ring OH-structure [88]. The –OH groups in these nuclei produce H_2 and give electron $(e)^-$ to OH, peroxyl, and peroxynitrite radicals to stabilize them and thus produce a stable flavonoid radical. The scavenging potential of a free radical is affected by the twisting angle of the B-ring as compared to the rest of the molecule. Higher antioxidant activity is related to the occurrence of –OH groups in ring B and then the total number of –OH groups present. According to Moalin *et al.*, quercetin and its compounds have strong antioxidant activity as compared to the other compounds [89]. Celik and Arinç found that quercetin has a higher antioxidant potential as compared to its flavonoid compounds (such as rutin and naringenin) [90]. Heijnen and coworkers discovered that –OH groups scavenge not only reactive O_2-species (ROS), but also reactive N_2 species (RNS). The flavonoids provide efficient protection against peroxynitrite toxicity. Two pharmacophores were identified in flavonoids which include hydroxyl group at the 3-position and the catechol group in ring B [91]. The antioxidant properties of flavonoids are dominated by their –OH groups. The hydroxyl group affects flavonoid 's ability to induce antioxidant enzymes [91]. Another research using Hepa-1c1c7 mouse hepatoma cells showed that flavonoids with 3-OH at the C-ring have significantly induced luciferase compared to flavonoids with no -OH-moiety [92].

Flavonoids' redox characteristics and antioxidant activity have been connected to the activation of the electrophile sensitive element which is a regulatory region of the genes producing phase II enzymes [93]. The value of 2,3-unsaturation in connection with a 4-C=O group has been demonstrated in several studies. According to Meyer *et al.*, electrons from the B ring are delocalized as a result of the existence of a 2,3-double bond in combination with the four-keto groups and cellular antioxidant function is substantially reduced when either or both of these nutrients are depleted [94]. This fact was cleared by comparing EC_{50} values of quercetin to catechin and taxifolin, as well as kaempferol to naringenin. The conjugation of the A and B rings creates a stable flavonoid radical due to resonance effect of the aromatic nucleus. O-methylation is another structure that contributes to the antioxidant potential. There are variations in antioxidant potential within flavonoids' structures. The differences in the values of hydrophobicity and molecular planarity are the main causes of different antioxidant potentials. In contrast to their unmethylated analogues, flavones with methylated moieties are metabolically stable and have greater intestinal absorption by human colon adenocarcinoma (Caco-2) cell monolayers. Wen *et al.* proposed that methylation protects these compounds from biotransformation in the liver [95].

Studies by using human oral SCC9 cancer cells confirmed that inhibitory potential of 5,7-dimethoxyflavone and 5,7,4-trimethoxyflavone is higher as compared to their unmethylated counterparts [96].

5.2 Structure-activity Relationship

Many natural flavonoids have been studied in this current research to establish a relationship between their structures and antioxidant activities. **Figure 3** demonstrates that there is close relation between the structures of flavonoids and their antioxidant activities. Antioxidant properties of flavonoids are calculated on the basis of positions of OH-groups, the B ring that has an ortho-dihydroxy arrangement, and the C skeleton where an unsaturated carbon-2 and carbon-3 bond is linked to a carbon-4 C=O group (**Figure 4**) [97, 98].

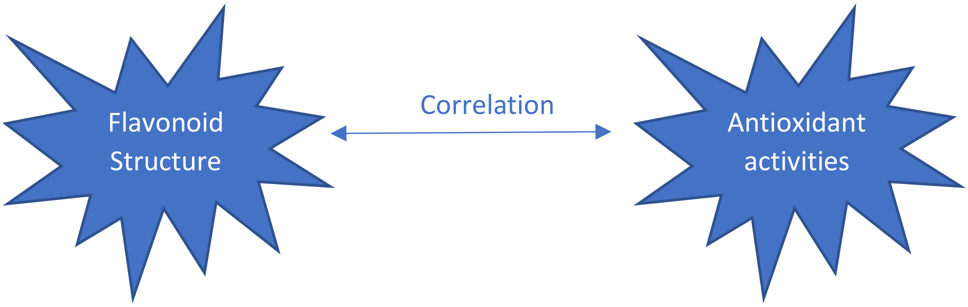


Fig 3. Correlation between flavonoid structure and antioxidant activities

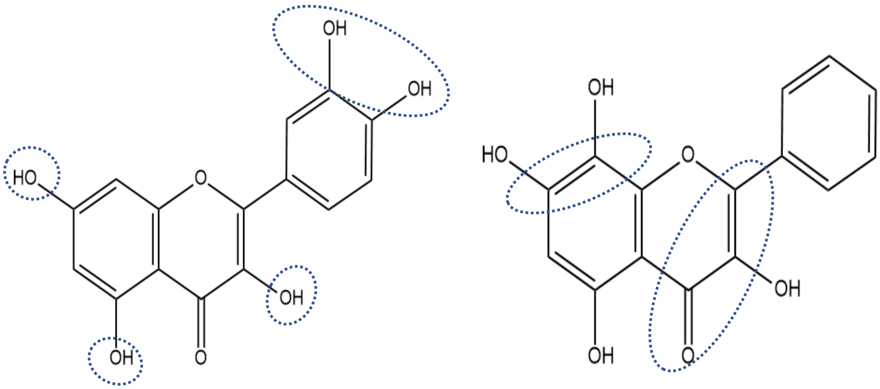


Fig 4. Flavonoids' antioxidant activity & their structural relationship

6. FLAVONOIDS AS NUTRACEUTICALS

The phenolic compounds from plants have an important role in human diet [99]. They cause organoleptic properties of plant-derived foods and are responsible for the development of taste and color. They also play an important role in the nutritional characteristics of vegetables and fruits. Flavonoids are important plant phenolics which are important not only for the human health and food organoleptic properties but also have a role in the prediction and controlling of food quality. They could be referred as nutraceuticals due to their nutritional and pharmacological potential in the mammalian body [100]. They are polyphenolic secondary metabolites which could be supplemented in a staple of food as nutraceutical agents [101]. Flavonoids possess diverse biological activities, including anti-inflammation, anti-oxidation, anti-cancer, anti-diabetes and anti-obesity. Their role in muscle atrophy has also been reported by monitoring molecular mechanisms which are involved myogenesis, mitochondrial activity, and protein turnover [102].

7. POTENTIAL USES OF FLAVONOIDS AGAINST DISEASES

Flavonoids possess many disease-preventive and health-promoting effects. Most important potential benefits are associated with their free-radical scavenging capacity and antioxidant activities. However, there are also numerous beneficial effects owing to their biological properties which include their neuroprotective, anticancer, antiviral, and anti-inflammatory activities [103]. Flavonoids have been linked to improved human health by curing different diseases and by chemoprevention. They have many beneficial antioxidant and biochemical properties which are connected to the treatment of different disorders such as atherosclerosis, cancer, and alzheimer's disease (AD) *etc* [104]. About 6 million people in the United States are affected by neurodegenerative diseases which include amyotrophic lateral sclerosis, huntington’s disease, parkinson’s disease, and alzheimer’s disease. Currently, there is no method which could prevent the progression and development of these diseases. Since, aging is an important factor which increases the risk of these diseases with large number of changes that take place in the brain so, the compounds flavonoids might get affected negatively and stop age-associated changes. Hence, this is useful to lower the development of neurodegenerative disease [105].

Flavonoids are essential pharmacological compounds which are linked to a wide range of health-promoting benefits. This is due to their ability to influence important cellular enzyme activities as well as their anti-inflammatory, anticarcinogenic, and antimutagenic capabilities. Flavonoids as a nutraceutical, have great antioxidant qualities that enables them to boost the amount of vitamin C in meals and protect the ascorbic acid from oxidizing. Green tea flavonoids have been reported as insulin analogues. Numerous flavonoids have been identified as having anti-cholinesterase properties. A number of enzymes, including lipoxygenase, cyclo-oxygenase (COX), lipoxygenase, and phosphoinositide 3-kinase, are also known to be effectively inhibited by flavonoids [106, 107].

Dietary flavonoids are known to reduce the risk of cardiovascular disease (CVD) and hypertension. A flavonoid-rich diet enhances vascular health and lowers the risk of illness. Many flavonoids have developed into bioactive substances with antibacterial and insecticidal capabilities by interacting with proteins or nucleic acids. Therefore, flavonoids are beneficial both in disease treatments and in agriculture as pesticides [108]. Some flavonoids exhibit hormone-like behaviour and show resemblance to steroid hormones [109]. Oestrogen, in particular, has neuroprotective effects on the brain and is well known for its ability to protect against a variety of chronic disorders such as cancer, heart disease, and osteoporosis [110]. According to clinical research, the flavonoid genistein showed a promising effect in reducing postmenopausal bone loss in women [111]. Flavonoids have beneficial effects on oxidative stress, inflammation, insulin resistance, and lipid metabolism which are the most important pathophysiological pathways in NAFLD. Flavonoids are food or food-derived compounds which are effective in the treatment of non-alcoholic fatty liver disease (NAFLD) which has currently no pharmacological treatment [112].

8. NEW DEVELOPMENTS FOR FLAVONOID DERIVATIVES

Over the past ten years, flavonoids have attracted a lot of interest in the research, and a number of potential benefits have been confirmed. For the structural optimization of bioactive molecules, the structural patterns of flavonoids need chemical adjustments to enhance their biological, physicochemical, and pharmacological features. Flavonoids would also serve as an adaptive template for the synthesis of new compounds having a variety of therapeutic applications. Therefore, further investigations are required to improve the usefulness of flavonoids to promote the human health. Due to the heterogeneity of the molecular structures and the accessibility of limited data on bioavailability, the studies on flavonoids were a challenging task. In particular, the insufficient information which existed for a longer-term effected the uses of flavonoid. Hence, there is a need to improve the information regarding their absorption, excretion, and analytical procedures [113].

Numerous reports have emphasized the need of molecular docking studies in order to find new flavonoid compounds for their usage in managing the chronic diseases. Furthermore, future studies could also focus on flavonoids' interactions with receptor molecules to treat both chronic and acute conditions [114]. Synthetic medications exhibit a large number of adverse effects, so future studies are required to find new flavonoids from natural sources. Research and development activities involving in *vivo* trials are required in order to improve the pharmacological effects of these compounds [58].

9. CONCLUSION

Flavonoids are secondary metabolites that occur naturally in plants as polyphenolic compounds. They are responsible for the taste and colors of medicinal plants e.g., berries, cherries, plums, apples, lemons, oranges, grapes, broad beans, olives, onions, spinach, shallot. They also exist abundantly in cocoa products, black and green tea, red wine, red pepper, chamomile, celery, parsley, ginkgo, and mint. Flavonoids could also be synthesized artificially through esterification, halogenation, alkoxylation, alkylation, aromatic hydroxylation, acylation, and conjugation with various organic compounds. They are an important part of food which demonstrate nutraceutical and pharmaceutical potential. They are affective in the treatment of cancer, diabetes, obesity, oxidative stress, inflammation, insulin resistance, lipid metabolism, and neurodegenerative diseases (for instance, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, and Alzheimer's disease). Their antioxidant potential could be owed due to the presence of –OH groups, differences in hydrophobicity, and molecular planarity. These flavonoids consist of a flavan nucleus and are classified into flavones, flavanols, isoflavones, flavan-3-ols, flavanonols, anthocyanidins, chalcones, and flavanones. They are effective chelating agents for metal ions which have the ability to scavenge free radicals. Therefore, molecular docking studies could be performed to find new flavonoid compounds for the management of various chronic diseases. Hence, this study investigated the sources and chemistry of flavonoids by analyzing their biological potential.

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